BioInvigor

{ Material Safety Data Sheet }

Revision Date : March 20,2004

I. Identification

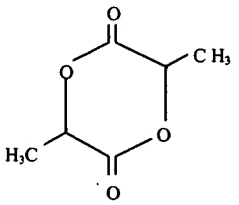
Chemical name : 3,6-dimethyl-1,4-dioxane-2,5-dione;1,4-dioxane-2,5-dione,polymer and copolymer thereof.

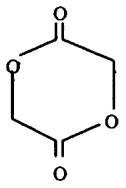
Chemical family : Polyester

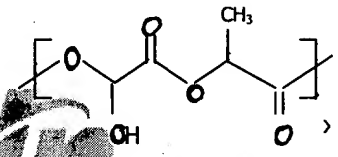
Common names : Polylactide, polylactic acid, PLA; Polyglycolide, Polyglycolic acid, PGA; Poly (lactide-co-glycolide), PLG .

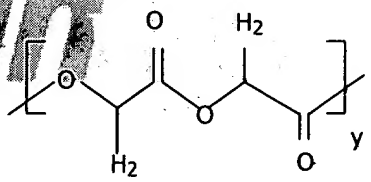
Chemical formula : $(C_6H_8O_4)x$, $(C_4H_4O_4)y$, $(C_6H_8O_4)x(C_4H_4O_4)y$.

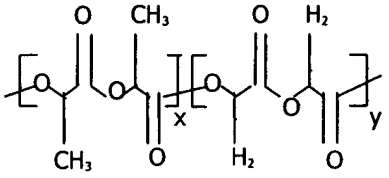
Chemical structure :

Lactide : 

Glycolide : 

Polylactide : 

Poly(glycolide) : 

Poly(lactide-co-glycolide) : 

II. Components

Material	CAS#	Hazard
L-lactide	4511-42-6	None known
DL-Lactide	615-95-2	None known
Glycolide	502-97-6	None known
Poly(DL-lactide)	26680-10-4	None known
Poly(L-lactide)	33135-50-1	None known
Poly(glycolide)	26202-08-4	None known
Poly(L-lactide-co-glycolide)	30846-39-0	None known
Poly(DL-lactide-co-glycolide)	26780-50-7	None known
Poly(L-lactide-co-DL-glycolide)	52305-30-3	None known

PLGA-PEG COPOLYMERS

Articles: PLGA-PEG Block Copolymers for Drug Formulations

By: Kang Moo Huh, PhD; Yong Woo Cho, PhD; and Kinam Park, PhD

ABSTRACT

Over the past few decades, biodegradable polyesters, such as poly(lactic acid) (F poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA), have been ext studied for a wide variety of pharmaceutical and biomedical applications. The biodegradable polyester family has been regarded as one of the few synthetic biodegradable polymers with controllable biodegradability, excellent biocompatibi high safety. The need for a variety of drug formulations for different drugs and de pathways resulted in development of various types of block copolymers (eg, diblc triblock, multiblock, and star-shaped block) consisting of the biodegradable polye and poly(ethylene glycol) (PEG). Extensive studies throughout the world have prc encouraging results demonstrating many desirable, unique properties of PLGA-P block copolymers. Despite successes in preclinical applications and ever-increas in diverse research activities, PLGA-PEG block copolymers are currently not ava commercially. Recognizing that demands for PLGA-PEG block copolymers in pharmaceutical and biomedical applications will continue to grow, Akina, Inc., (www.akinainc.com/polycelle) has started production of PLGA-PEG block copolyı those who want to use the block copolymers but are not willing to synthesize ther This article describes synthesis of PLGA-PEG block copolymers and their applica drug delivery vehicles, such as micro/nano-particles, micelles, hydrogels, and inje delivery systems.

INTRODUCTION

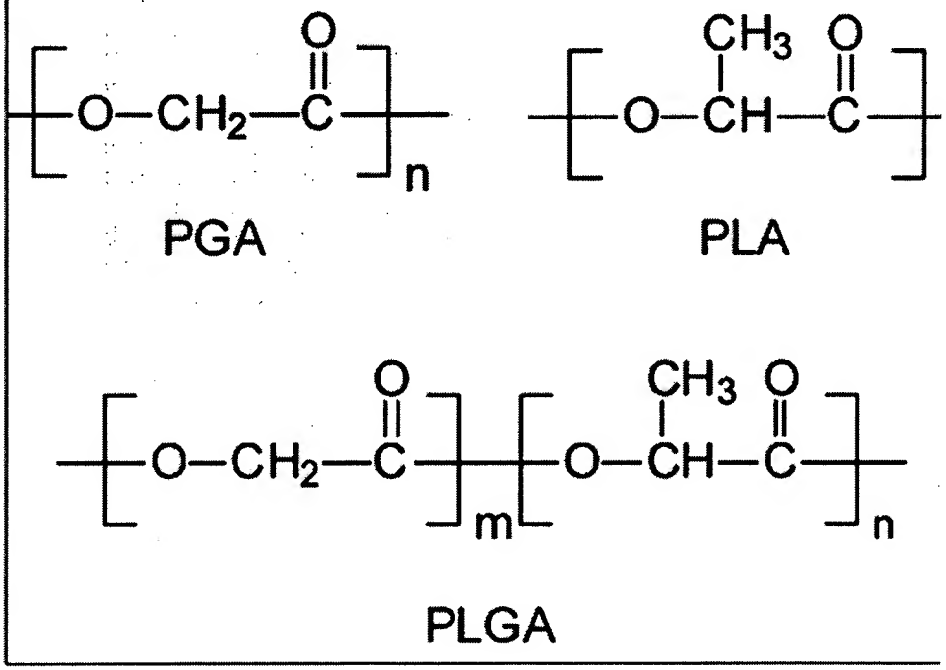
Recently, biodegradable polymers, especially poly(lactic acid) (PLA), poly(glycoli (PGA), and poly(lactic-co-glycolic acid) (PLGA), have been used significantly in pharmaceutical and biomedical applications. Poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid) have also been called polylactide, polyglycolide, and (lactide-co-glycolide), respectively, according to the nomenclature system based source of the polymer. Although these names were used in many references in tl a recent trend is to follow the nomenclature system of the International Union of F Applied Chemistry (IUPAC) that is based on the repeating unit structure. PLA, PC PLGA can be degraded into non-toxic substances and removed from the human Accordingly, they have taken center stages in a variety of research efforts.

The biodegradable polyesters are all strongly hydrophobic, and this has caused s limitations in practical drug formulations. To add hydrophilic and other physico-ch properties, poly(ethylene glycol) (PEG) has been incorporated into the biodegrad polyesters. PEG is a non-toxic, water-soluble polymer with proven biocompatibilit copolymers consisting of a hydrophobic polyester segment and a hydrophilic PEC segment have attracted large attention due to their biodegradability, biocompatibi tailor-made properties. A wide variety of drug formulations, such as micro/nano-p

micelles,[2] hydrogels,[3] and injectable drug delivery systems[4] have been develope PLGA-PEG block copolymers. They have been extensively investigated for use i range of applications, including implantable materials, drug delivery systems, anc engineering scaffolds. They are very useful materials for pharmaceutical and bio applications, and thus they have significant commercial potential. Demands for th copolymers will continue to grow, and they are expected to build a great market a precursors, such as PLA, PGA, and PLGA, did. This review includes synthetic m PLGA-PEG block copolymers and their applications in controlled drug delivery. I addition, availability and significance of commercial production of the block copo are briefly described.

FIGURE 1

Chemical structure of poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and poly(lactic-co-glycolic acid) (PLGA).



PLA, PGA & PLGA AS BIOMATERIALS

Biodegradable polymers have been extensively used in controlled drug delivery. have the advantage of not requiring surgical removal after they serve their intend purposes. PGA, PLA, and especially their copolymers PLGA are the most comm used family of biodegradable polymers. PGA was used as a biodegradable sutur material in the 1970s, and it has led the largest volume production in the biomedi polymer markets, when its production was combined with those of PLA and PLG then, they have found a broad range of pharmaceutical and biomedical applicatio based on their unique properties, including versatile degradation kinetics, non-to and biocompatibility.[6] The general properties and typical applications of PGA, PL PLGA are summarized in Table 1.

Table 1. **Properties and applications of PGA, PLA, and PLGA[1,2]**

Polymer	Crystallinity	T_g(°C)	Degradation Rate[a]	Typical applications
PGA	Highly crystalline (T_m=225~230°C)	35 ~ 40	2-3 months	Suture, Soft anaplerosis
PLA (L form)	Semicrystalline (T_m=173~178°C)	60 ~ 65	> 2 years	Fracture fixation, Ligament augmentation
PLA (D, L form)	Amorphous	55 ~ 60	12-16 months	Drug delivery system
PLGA	Amorphous	45 ~ 55	1-6 months[b]	Suture, Fracture fixation, Ora implant, Drug delivery microsphere

a. Rate depends on molecular weights of the polymers.
b. Rate may change according to the ratio of LA and GA.

PGA is a highly crystalline polymer and the most hydrophilic among them. It has a high melting point (224°C to 226°C), and the degradation rate of PGA is much hig than that of PLA. Random PLGA copolymers with different ratios of lactide (LA) a glycolide (GA) exhibit different degradation rates, and thus can be tailor-made for applications requiring specific degradation kinetics ranging from weeks to months are generally more amorphous than their homo-polymers and become most susc to hydrolysis when the two monomer contents are the same.

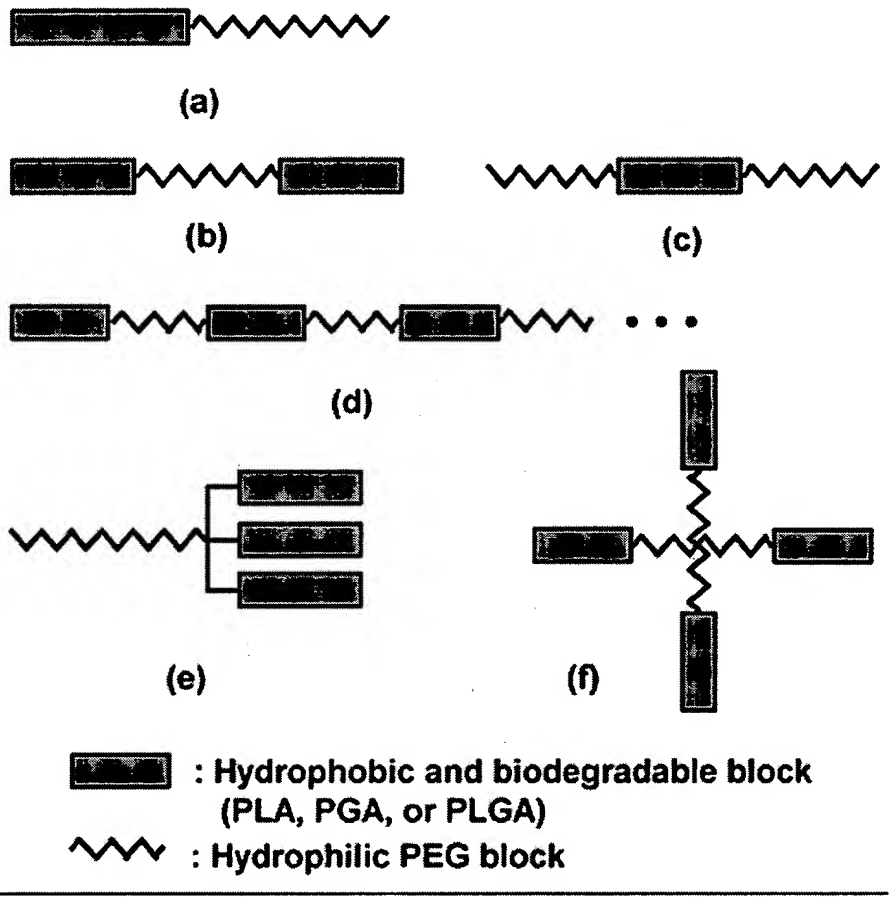
SYNTHESIS OF PLGA-PEG BLOCK COPOLYMERS

One useful strategy for modifying the physicochemical and biological properties c hydrophobic and biodegradable PLA, PGA, and PLGA has been to incorporate hydrophilic PEG segments. It is known that low molecular weight PEGs are easily excreted in humans. Many synthetic methods were developed to prepare various block copolymers with different block structures and compositions.

The biodegradation rate and hydrophilicity of block copolymers can be modulatec adjusting the ratio of its hydrophilic and hydrophobic constituents. Usually, PLGA block copolymers have shown quite different properties when compared to each constituting polymer. For this reason, PLGA-PEG block copolymers became a ne of biomaterials with their own unique properties, such as microphase separation, crystallinity, water-solubility, and biodegradability. Various kinds of block copolym have been developed to date and can be classified according to their block struct AB diblock,[7] ABA,[1,8] or BAB[4,9] triblock, multi-block,[10,11] branched block,[12] star-sh block,[13] and graft block[14] copolymers, in which A is a hydrophobic block made up biodegradable polyesters and B is a hydrophilic PEG block, as shown in Figure 2

FIGURE 2

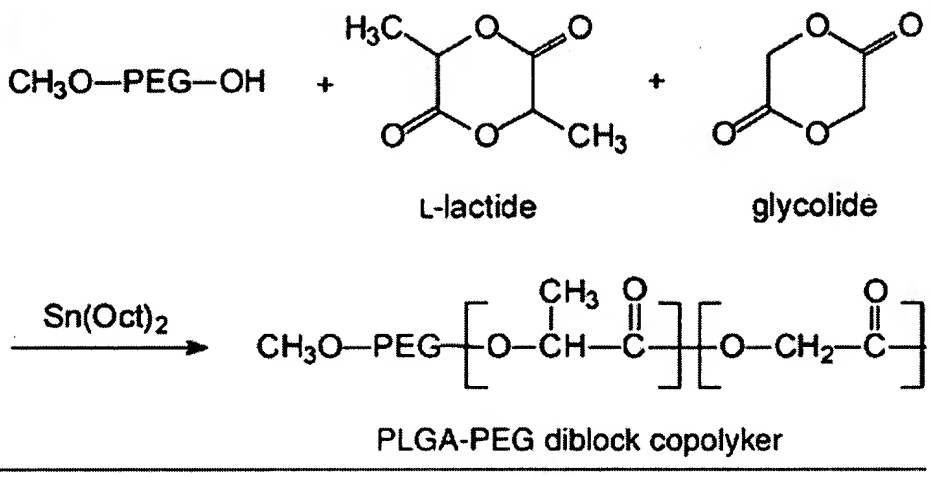
Schematic presentation of block copolymer structures: (a) A-B diblock, (b) A-B-A, (c) B-A-B, (d) alternating multiblock, (e) multi-armed structure, and (f) star-shaped block.



Homo- and copolymers of LA and GA are usually synthesized by ring-opening polymerization of cyclic monomers. The block copolymers can be synthesized us various kinds of different catalysts, but also in the absence of catalysts. One of th widely used catalysts is stannous octoate. Figure 3 shows a typical example for s of PLGA-PEG block copolymers using stannous octoate. The terminal hydroxyl g PEG have been used as the initiating groups to synthesize block copolymers. Th ring opening polymerization of lactide and glycolide initiated by dihydroxy PEG or monomethoxy PEG can lead to A-B-A or A-B type block copolymers, respectively type block copolymers can be obtained by coupling the diblock copolymers using hexamethylene diisocyanate. Alternating multiblock copolymers of PLA and PEG synthesized by polycondensation reaction between dihydroxy PEG and dicarboxy PLA.[10] Dicarboxylated oligomeric PLAs were synthesized as macro-monomers b condensation reaction of lactic acid in the presence of succinic acid. Kissel et al. star-shaped block copolymers from multi-arm PEG and lactide or lactide/glycolide Biodegradable star-shaped PLA-PEG and PLGA-PEG block copolymers can be synthesized by ring opening polymerization in the presence of 4- or 8-branched P using aluminum triethylene as a catalyst.

FIGURE 3

A typical synthetic route of a PLGA-PEG diblock copolymer.



PROPERTIES OF PLGA-PEG BLOCK COPOLYMERS

One typical characteristic of PLGA degradation is autocatalysis by which heterog bulk degradation is observed with a decrease in pH. Carboxylic end groups of de products, oligomeric PLGA, can accelerate the degradation and decrease the loc PLGA formulations. This locally acidified environment is known to be a main reas protein inactivation and often requires incorporation of antacids, such as Mg(OH) the polymers for protein stabilization by neutralization.[16] In addition, other limitati such as hydrophobicity, brittleness, and toxicity, have been reported with PLGA formulations. Block copolymers containing hydrophilic PEG segments have attrac considerable attention as an alternative approach for overcoming such undesirab effects and improving the properties in applications of PLGA as drug delivery veh Through various synthetic processes, diverse block copolymers with a wide rang molecular weights, chemical structure, and hydrophilic/hydrophobic block ratios h been prepared and used in controlled drug delivery.

The chemical composition and molecular weight of block copolymers determines water-solubility and degradation kinetics. Polymers with low molecular weight or composed of shorter hydrophobic blocks are soluble in water, whereas high mole weight polymers and polymers with longer hydrophobic blocks are not soluble bu water. In general, the degradation time will be shorter for low molecular weight pc more hydrophilic polymers, more amorphous polymers, and copolymers with higl content of glycolide. Therefore, at identical conditions, low molecular weight copc of lactide and glycolide will degrade relatively rapidly, whereas the high molecula homopolymers, PLA, and PGA will degrade much more slowly.

PLGA-PEG BLOCK COPOLYMERS IN DRUG FORMULATIONS

Various types of drug formulations, such as nano/micro-particles, hydrogels, mice and injectable delivery systems have been developed using PLGA-PEG block copolymers to deliver hydrophobic drugs as well as hydrophilic peptide and prote The ability of the polymers to entrap drugs and subsequently release them at a c rate has been used to develop various drug formulations.

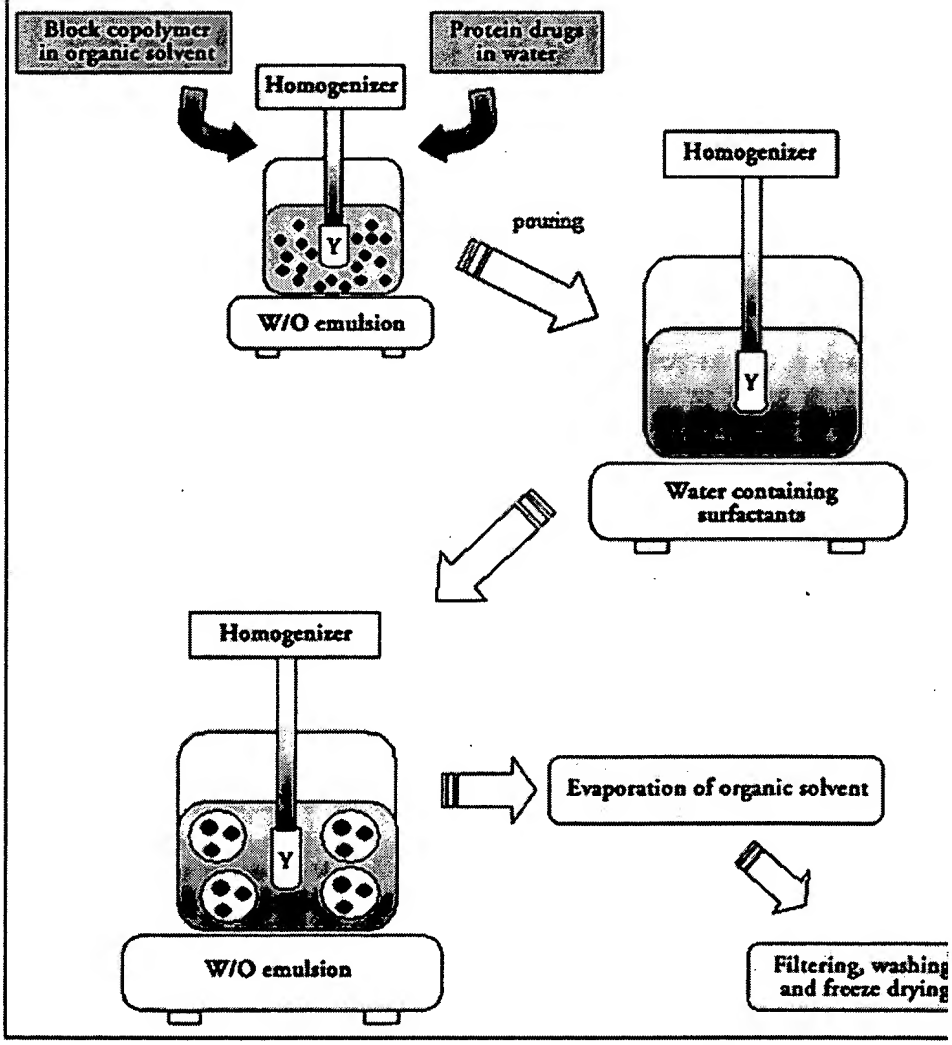
Nano/Microparticles

ABA triblock copolymers are more hydrophilic than PLA or PLGA itself, and are considered more suitable for development of delivery systems for hydrophilic

macromolecular drugs, such as peptides, proteins, and oligo/polynucleotides. Mic nano-particles prepared from AB diblock and ABA triblock copolymers are extens investigated for protein drug delivery.[1,17-19] Block copolymer nano/microparticles generally prepared by water/oil/water (W/O/W) double emulsion method, as show Figure 4. The W1 phase, an aqueous phase containing protein drugs, is disperse the oil phase consisting of polymer dissolved in organic solvent (eg, dichlorometh using a high-speed homogenizer. The primary water-in-oil (W/O) emulsion is ther dispersed to an aqueous solution containing a polymeric surfactant, eg, poly(viny alcohol) (PVA), and further homogenized to produce a W/O/W emulsion. After sti several hours, the nano/microparticles are collected by filtration. They show quite different release patterns when compared with PLGA. Kissel at al. reported that A triblock copolymers showed a continuous and molecular mass-dependent releas the release from PLGA was biphasic and almost independent of the molecular m entrapped substances.[8]

FIGURE 4

Schematic representation of a general procedure for PLGA-PEG block copolymer nano/microparticles.



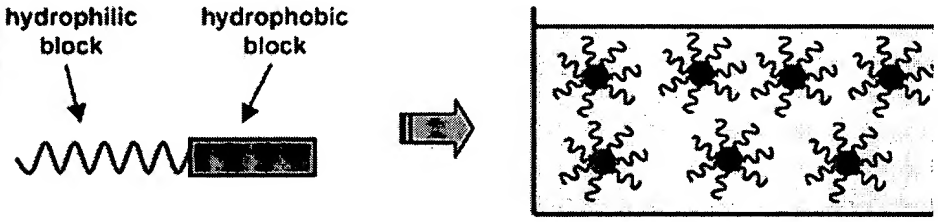
Polymeric Micelles

Amphiphilic PLGA-PEG block copolymers form micelles composed of a hydrophc

PLGA core and hydrophilic PEG shell in water, as shown in Figure 5. Hydrophob are segregated from the aqueous exterior to form an inner core surrounded by a of hydrophilic segments. Block copolymer micelles are water-soluble, biocompati nanocontainers in the size of 10~100 nm with proven efficacy of delivering hydro drugs. These micelle-forming block copolymers can provide high concentration o hydrophobic drugs with increased drug stability in an aqueous milieu above the s limit of the drug. The ability of polymeric micelles to target certain cells (eg, cance can also lower the required dosage.[20] The size and morphology of block copolym micelles can be easily changed by adjusting the chemical composition, total mole weight, and ratio of the block lengths. Various hydrophobic drugs, including paclit have been incorporated into the hydrophobic inner core of micelles.

FIGURE 5

Self-assembly of amphiphilic block copolymers to a micellar structure in aqueous solution.



Single block copolymer Polymeric micelles in aqueous me

Hydrogels

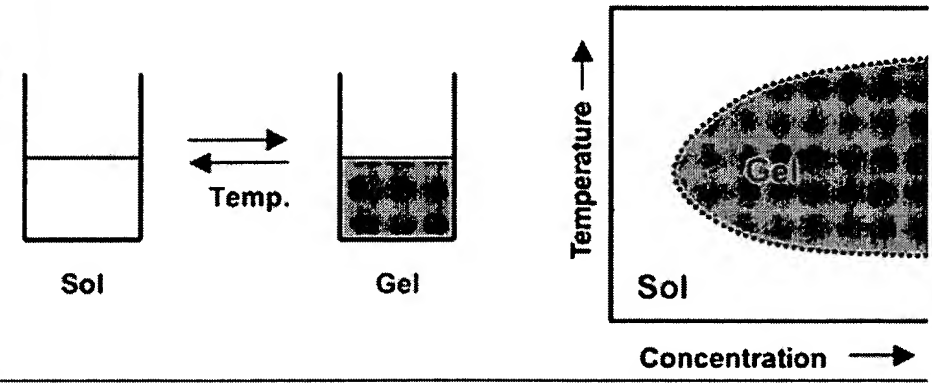
When the block copolymers have high molecular weights and high PLGA content become water-insoluble but can swell in water. Block copolymers consisting of hydrophilic and hydrophobic blocks are able to form physical crosslinking in an a environment through hydrophobic interaction, crystalline microdomains or chain entanglement.[3] Physical associations of hydrophobic domains maintain swollen s domains together and keep the polymer network stable in water. Although physic associations are reversible and weaker than chemical crosslinking, they allow sol casting and thermal processing, and the resulting polymer gels often possess ela viscoelastic properties. These biodegradable, physical hydrogels may offer an alt material of choice in designing drug delivery systems as well as other biomedical applications.[11]

Injectable Drug Delivery Systems

Aqueous solutions of low molecular weight B-A-B type triblock copolymers are w known to have thermo-reversible sol-gel transitions, forming in situ hydrogels wit harmful organic solvents or any chemical reactions.[4,9,21] Figure 6 schematically represents the thermo-reversible sol-gel transition of the triblock copolymers. The can be loaded with drugs in aqueous phase at low temperature (below critical gel temperature) where it forms a sol. Just following subcutaneous injection, the elev temperature to 37°C (above critical gelation temperature) makes the injected sol that can act as a sustained-release matrix for the loaded drugs. Thermo-reversibl hydrogels have recently attracted large attention due to the simplicity of drug form by solution mixing, biocompatibility with biological systems, and convenient administration. Pharmaceutical and biomedical applications of the block copolym include solubilization of low molecular weight hydrophobic drugs, controlled relea labile biomacromolecules (eg, proteins and genes), cell immobilization, and tissu engineering.

FIGURE 6

Thermo-reversible sol-gel transition of an amphiphilic block copolymer solution and its typical phase diagram.



LACK OF COMMERCIAL SOURCES FOR PLGA-PEG BLOCK COPOLYMERS

Biodegradable polymers have been playing a key role in various pharmaceutical biomedical research and product development. Materials that can degrade and d from the body are desirable for a number of applications, including orthopedics, ti engineering, and controlled drug delivery systems. For this reason, a number of commercial sources supply PLA, PGA, and PLGA throughout the world. Howeve are no commercial sources supplying block copolymers consisting of hydrophobi of PLA, PGA, or PLGA and hydrophilic PEG blocks. These block copolymers hav properties that homopolymers cannot provide, and are ideal for formulating contr drug delivery systems and for making scaffolds for tissue engineering. Yet their commercial introduction has not been made to date. Demands for these block copolymers are expected to grow as the pharmaceutical and biomedical fields co grow.

COMMERCIAL PRODUCTION OF PLGA-PEG COPOLYMERS

During the past few decades, significant advances have been made in polymeric delivery technology. Drug delivery in the future will need more sophisticated and formulations for existing drugs as well as new drugs, such as protein and peptide Biodegradable polymers have an important role in the development of controlled- formulations. PLGA-PEG block copolymers have a number of unique and useful properties that are ideal for controlled drug delivery. The properties of sol-gel trar well-defined temperatures and biodegradability make block copolymers an ideal vehicle for various drugs, including protein drugs. Numerous new protein drugs a expected in the near future as a result of an increased understanding of genomic proteomics. Thus, demands for the PLGA-PEG block copolymers are expected t exponentially for both research and product development in the coming years. To the current needs and prepare for the future demands, Akina, Inc., started produc biodegradable PLGA-PEG block copolymers for those who wish to use them in th research and development of drug delivery systems (www.akinainc.com/polycelle

Synthetic methods for the block copolymers are well established, and Akina prod block copolymers consisting of glycolide, lactide, and PEG. These three main bui blocks can be assembled into a wide variety of different combinations to synthesi copolymers with diverse, but tailor-made, properties. Properties, such as degrad rate, hydrophilicity, cystallinity, and solubility, can be easily custom-made for spe applications.

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BIOGRAPHIES

Dr. Kang Moo Huh is a Principal Scientist at Akina, Inc., where he is engaged in research projects related to the development of biodegradable block copolymers superporous hydrogels for drug delivery and tissue engineering applications. Dr.

earned his BS in Polymer Science and Engineering from Chungnam National Un (South Korea), his MS in Materials Science and Engineering from Kwangju Institu Science and Technology (South Korea), and his PhD in the School of Materials S from Japan Advanced Institute of Science and Technology (Japan). He complete Post-doctoral research at the Biomedical Center of Korea Institute of Science anc Technology, where he participated in the development of polymeric gene carriers injectable hydrogels. Research interests include design and synthesis of stimuli-s polymers and hydrogels, polymeric micelles as delivery carriers for hydrophobic c biodegradable amphiphilic block copolymers, and supramolecular-structured hyd using host-guest interactions for biomedical applications.

Dr. Yong Woo Cho is a Principal Scientist at Akina, Inc., where he is involved in research projects on the development of polymeric micellar carriers for poorly sol drugs and RNA enzyme delivery systems. He has considerable experience in the of biopharmaceutical formulation development, anti-tumor drug delivery, gene de and tissue engineering. Dr. Cho earned his BS, MS, and PhD in the Department and Polymer Science from Seoul National University, Seoul, Korea. He worked fc Korea Institute of Science and Technology as a Post-doctoral research associate he performed research projects on development of anti-tumor drug delivery syste regeneration of defected tissues and organs, and development of antibiotics-rele urethral catheters. Dr. Cho's recent research interests include polymeric self-ass biomimetic materials, and functional delivery systems to induce endosomal escaj genomics-based pharmaceuticals.

Dr. Kinam Park is the Founder of Akina, Inc., specializing in drug delivery techn He is also Professor in the Departments of Pharmaceutics and Biomedical Engin Purdue University. Dr. Park earned his PhD in Pharmaceutics from the University Wisconsin in 1983. Following his Post-doctoral training in the Department of Che Engineering at the same university, he joined the faculty of Purdue University. Si 1998, he has the joint appointment in the Department of Biomedical Engineering. current work at Akina is focused on development of controlled-release protein de systems using PLGA-PEG block copolymers, diet control aids using biodegradab superporous hydrogels, layer-by-layer coating technology for drug-eluting stents, novel technology for developing fast-melting tablets.